

MDTKHFLPLDFSTQVNSSLTSPTGRGSMAAPSLHPSLGP GIGSPGQLHSPISTLSSPINGMG
PPFSVISSPMGPHSMSVPTTPTLGFSTGSPQLSSPMNPVSSSEDIKPPLGLNGVLKVPAPHS
GNMASFTKHICAICGDRSSGKH YGVYSCEGCKGFFKRTVRKDLTYTCRDNKDCLIDKRQRNR
CQYCRYQKCLAMGMKREAVQEERQRGKDRNENEVESTSSANEDMPVERILEAELAVEPKTET
YVEANMGLNPSSPNDPVTNICQAADKQLFTLVEWAKRIPHFSELPLDDQVILLRAGWNELLI
ASFHSRSIAVKDGILLATGLHVHRNSAHSAGVGAI FDRVLTEL VSKMRDMQMDKTELGCLRA
IVLFNPDSKGLSNPAEVEALREKVYASLEAYCKHKYPEQPGRF AKLLLRLPALRSIGLKCLE
HLFFFKLIGDTPIDTFLMEMLEAPHQMT

FIGURE 1A

MSWAARPPFLPQRHAAGQCGPVGVRKEMHCGVASRWRRRRPWLD PAAAAAAAVAGGEQQTPE
PEPGEAGRDGMGDSGRDSRSPDSSSNPLPQGVPPPSPPGPPLPPSTAPSLGGSGAPPPPPM
PPPPLGSPFPVISSSMGSPGLPPPAPPGFSGPVSSPQINSTVSLPGGSGPPEDVKPPVLGV
RGLHCPPPP GPGGAGKRLCAICGDRSSGKH YGVYSCEGCKGFFKRTIRKDLTYSCRDNKDCT
VDKRQRNRCQYCRYQKCLATGMKREAVQEERQRGKDKDGDGEGAGGAPEEMPVDRILEAELA
VEQKSDQGVGPGGTGGSGSSPNDPVTNICQAADKQLFTLVEWAKRIPHFSSLPLDDQVILL
RAGWNELLIASFSHSRIDVRDGILLATGLHVHRNSAHSAGVGAI FDRVLTEL VSKMRDMRMD
KTELGCLRAIILFNPDAKGLSNPSEVEVLREKVYASLE TYCKQKYPEQQGRFAKLLLRLPAL
RSIGLKCLEHLFFFKLIGDTPIDTFLMEMLEAPHQLA

FIGURE 1B

MYGNYSHFMKFPAGYGGSPGHTGSTMSPSAALSTGKPMDSHPSYTDTPVSAPRTL SAVGTP
LNALGSPYRVITSAMGPPSGALAAPPGINLVAPPSSQLNVVNSVSSSEDIKPLPGLPGIGNM
NYPSTSPGSLVKHICAICGDRSSGKH YGVYSCEGCKGFFKRTIRKDLIYTCRDNKDCLIDKR
QRNRCQYCRYQKCLVMGMKREAVQEERQRSRERA ESEAECATSGHEDMPVERILEAELAVEP
KTESYGDMNMENSTNDPVTNICH AADKQLFTLVEWAKRIPHFSDLTLEDQVILLRAGWNELL
IASFSHSRSVSVDGILLATGLHVHRSSAHSAGVGSIFDRVLTEL VSKMKDMQMDKSELGCLR
AIVLFNPDAKGLSNPSEVETLREKVYATLEAYTKQKYPEQPGRF AKLLLRLPALRSIGLKCL
EHLFFFKLIGDTPIDTFLMEMLETPLQIT

FIGURE 1C

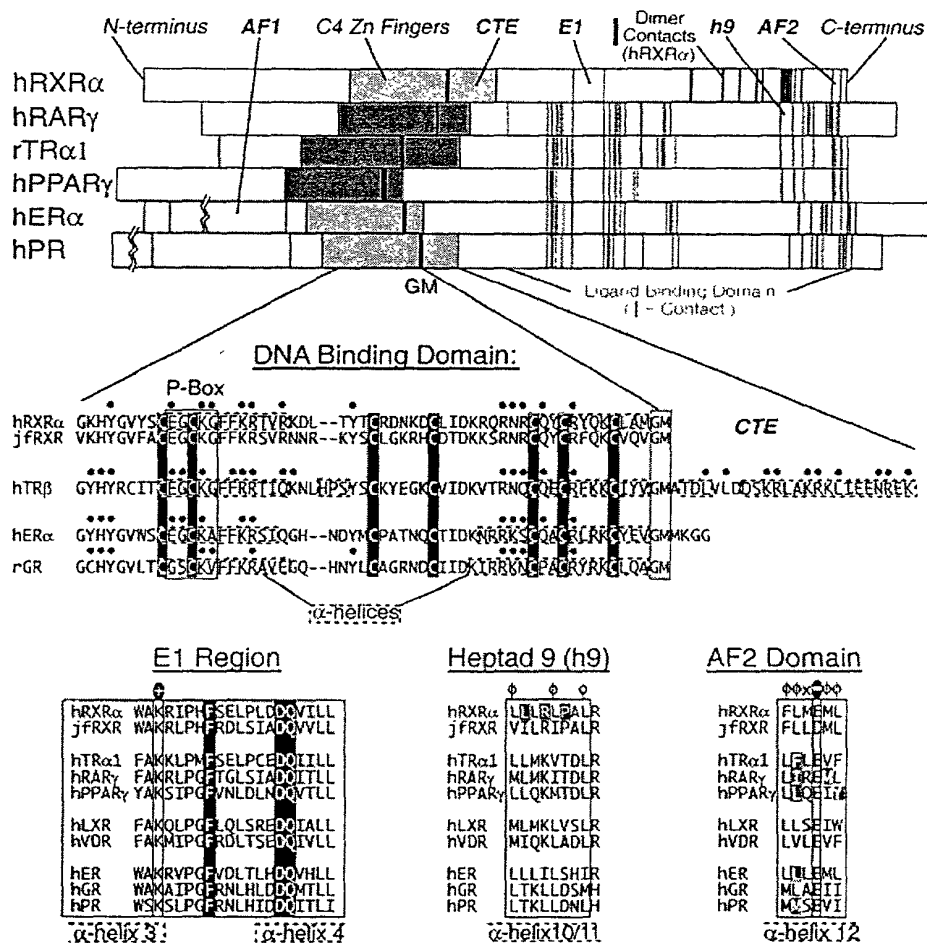


FIGURE 2

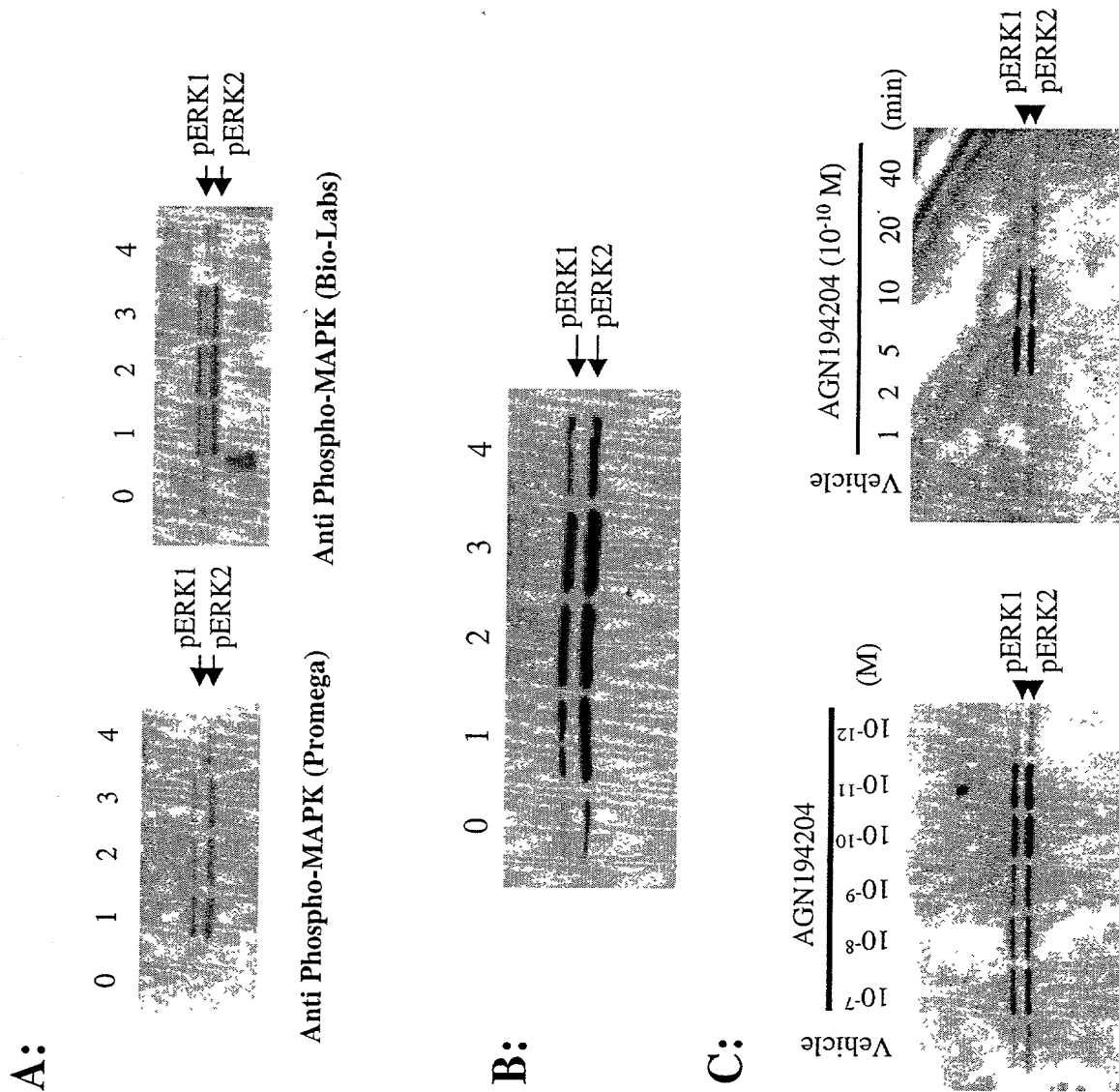


FIGURE 3

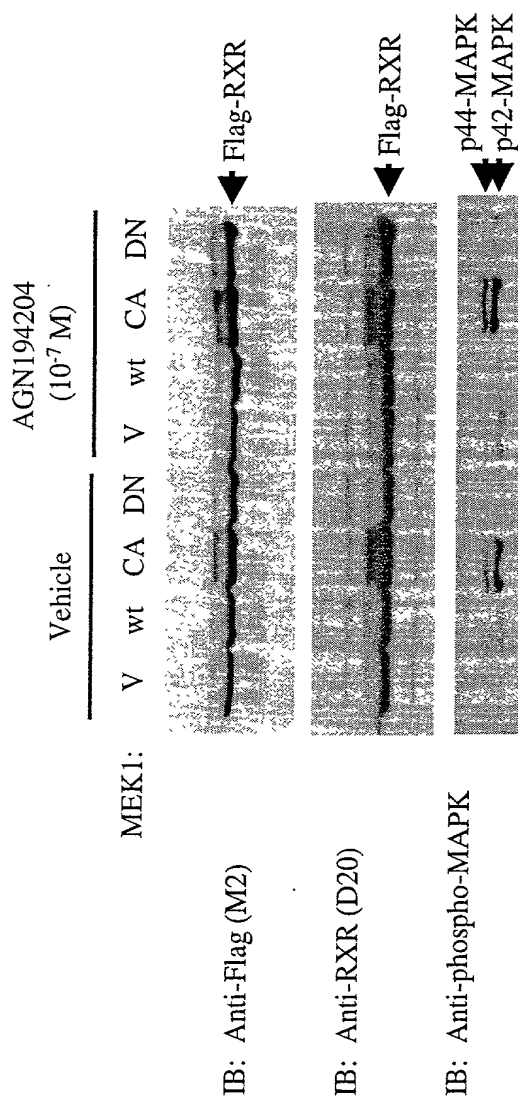


FIGURE 4

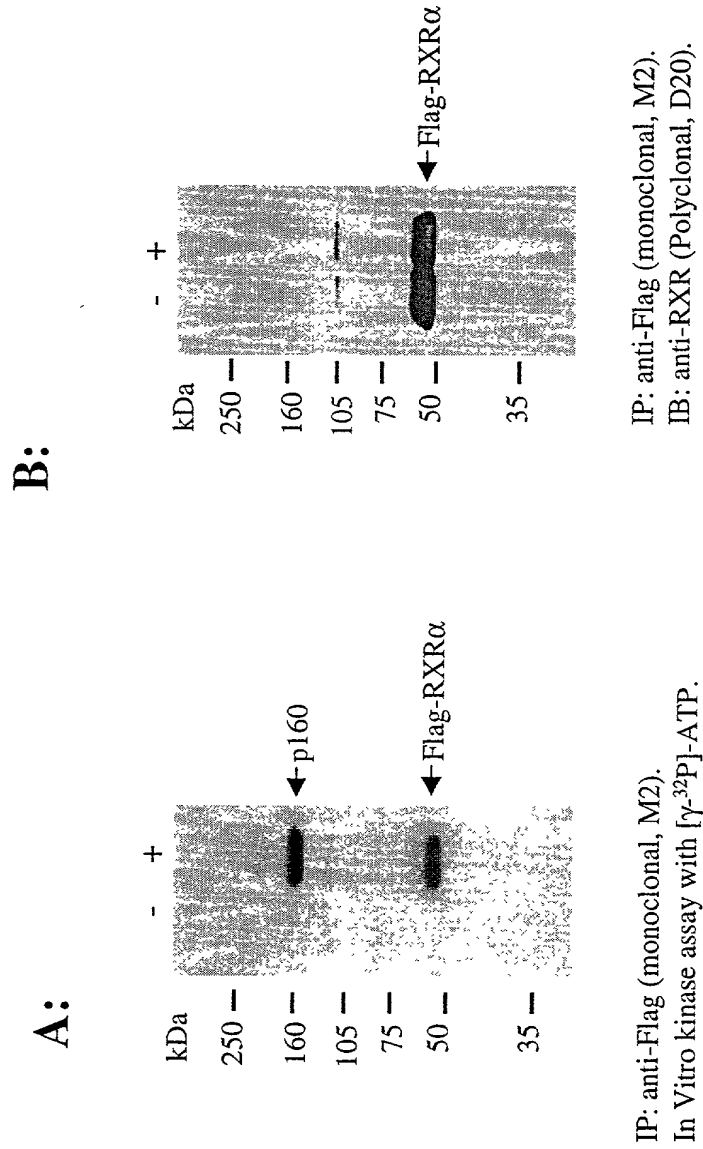
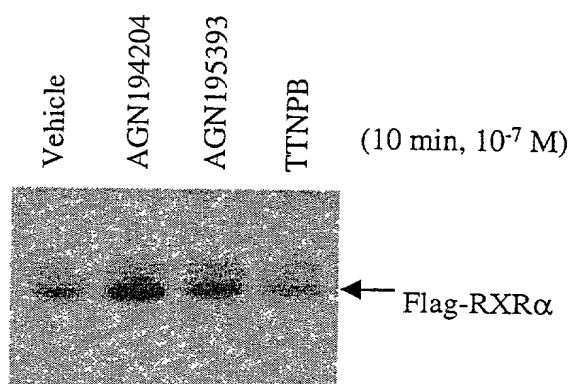


FIGURE 5

C:



In vivo labeling with [32 P]ortho-phosphate.

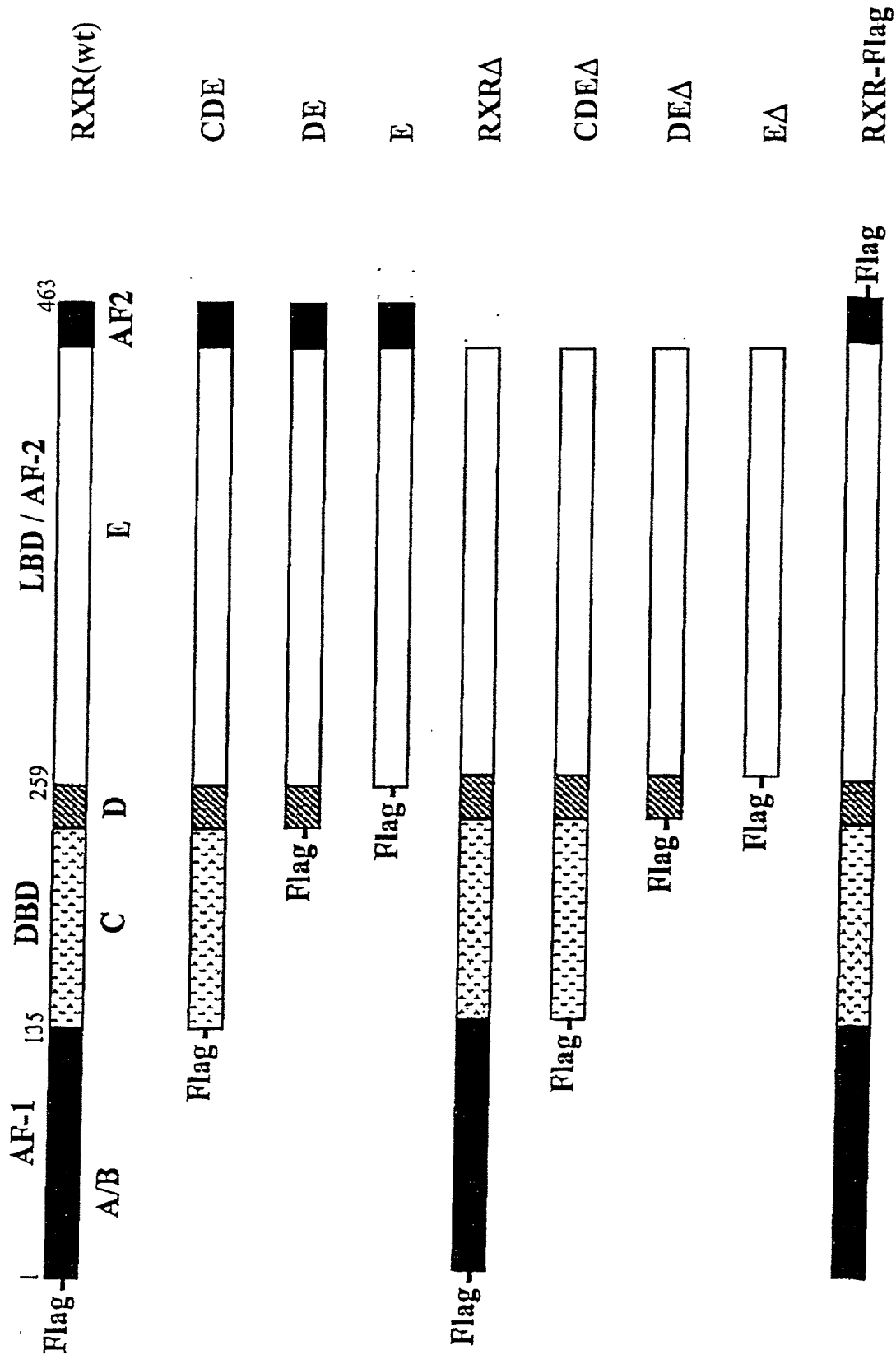


FIGURE 7

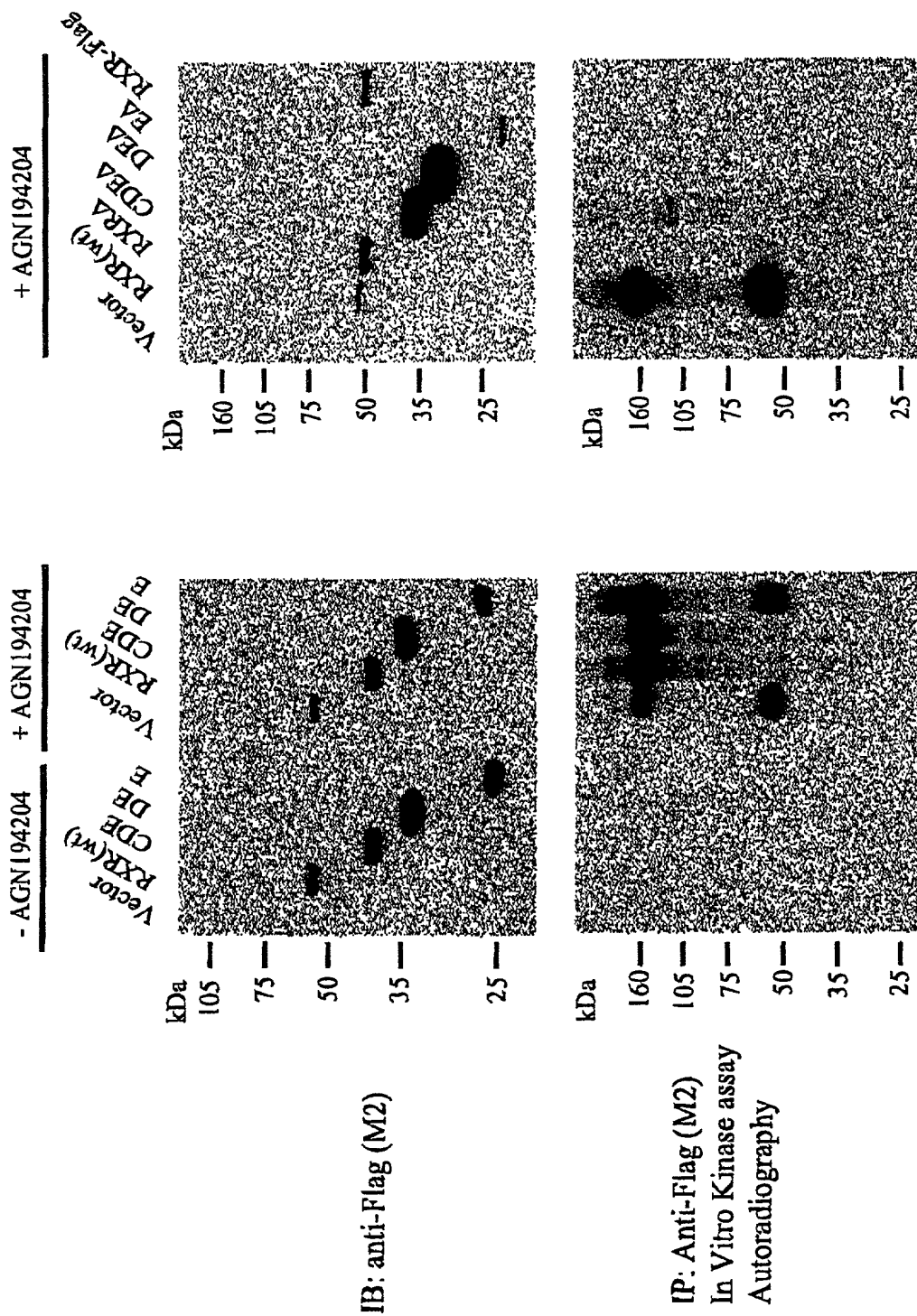


FIGURE 8

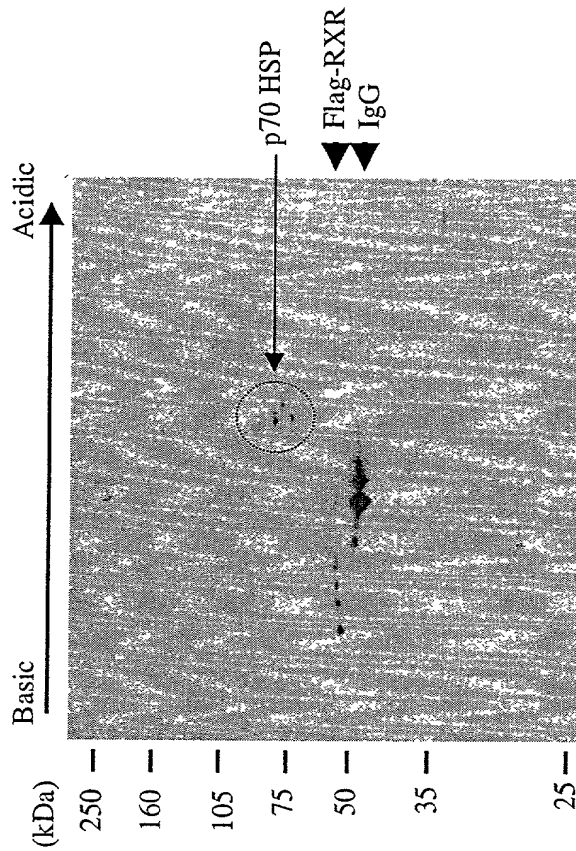


FIGURE 9

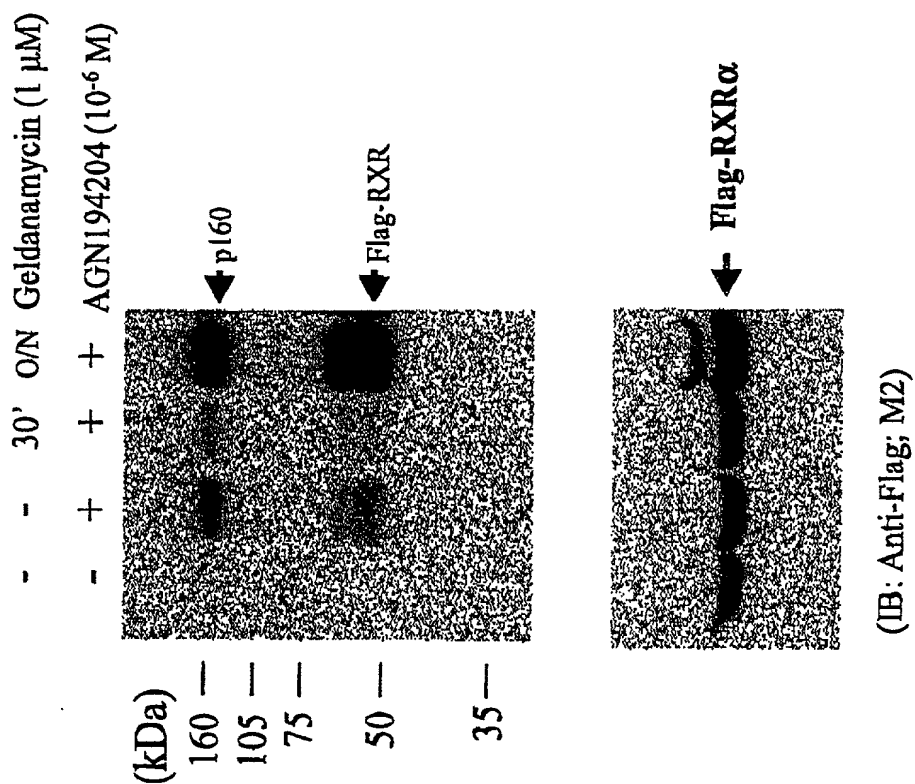


FIGURE 10

AGN194204

 (10^{-7} M)

Vehicle

MEK1:

NC

wt

$$\mathbf{V}$$

II

wt

V

▼ p160

▼ Flag-RXR

p44-MAPK
p42-MAPK

IP: Anti-Flag (M2)
In vitro Kinase Assay

FIGURE 11

B:

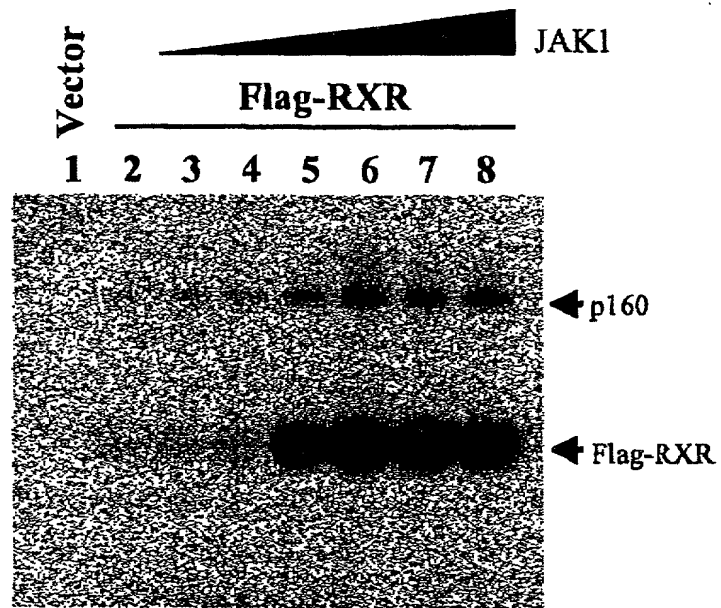
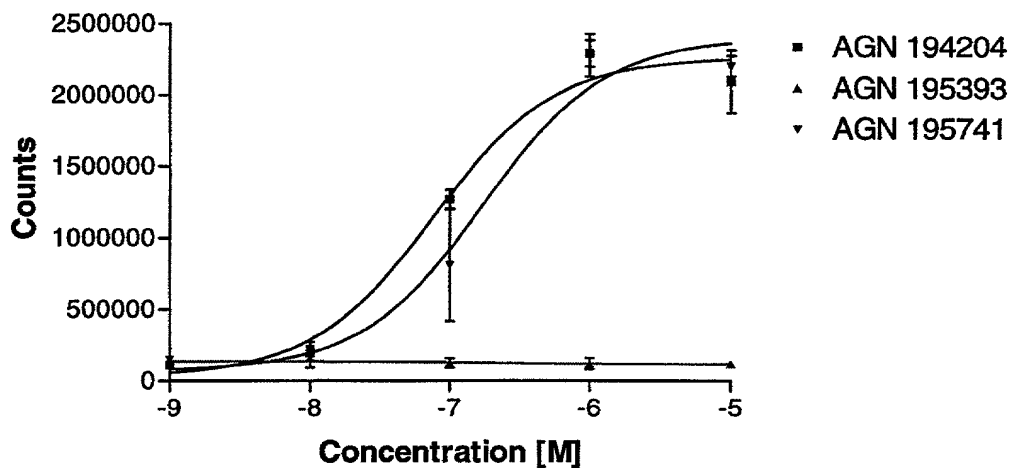


FIGURE 11 CONTINUED

A



B

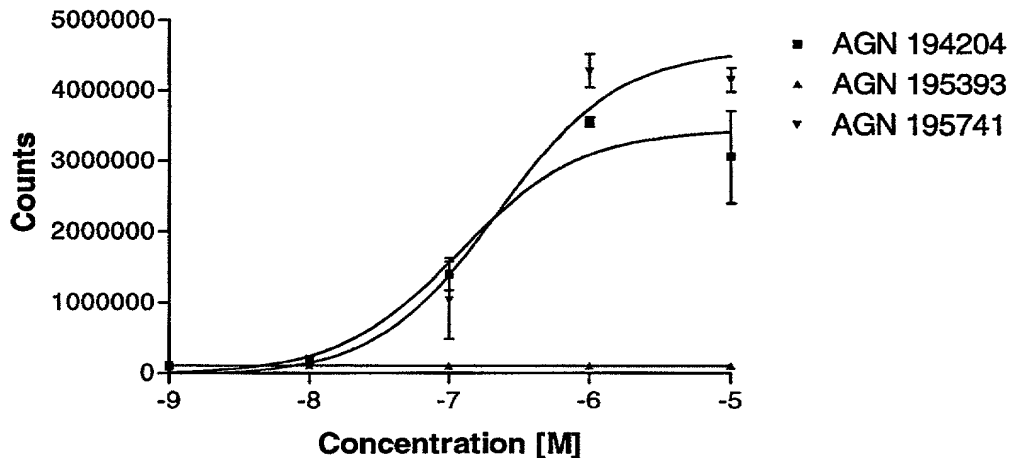


FIGURE 12

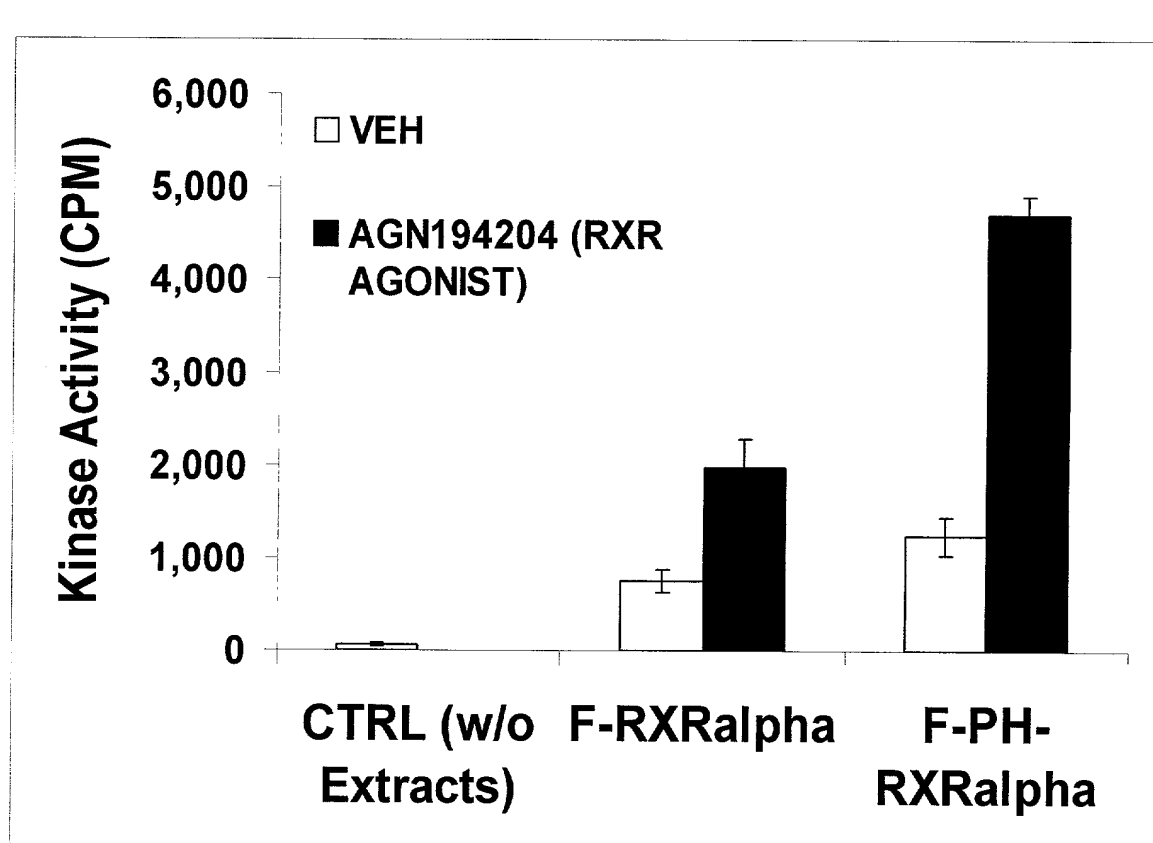
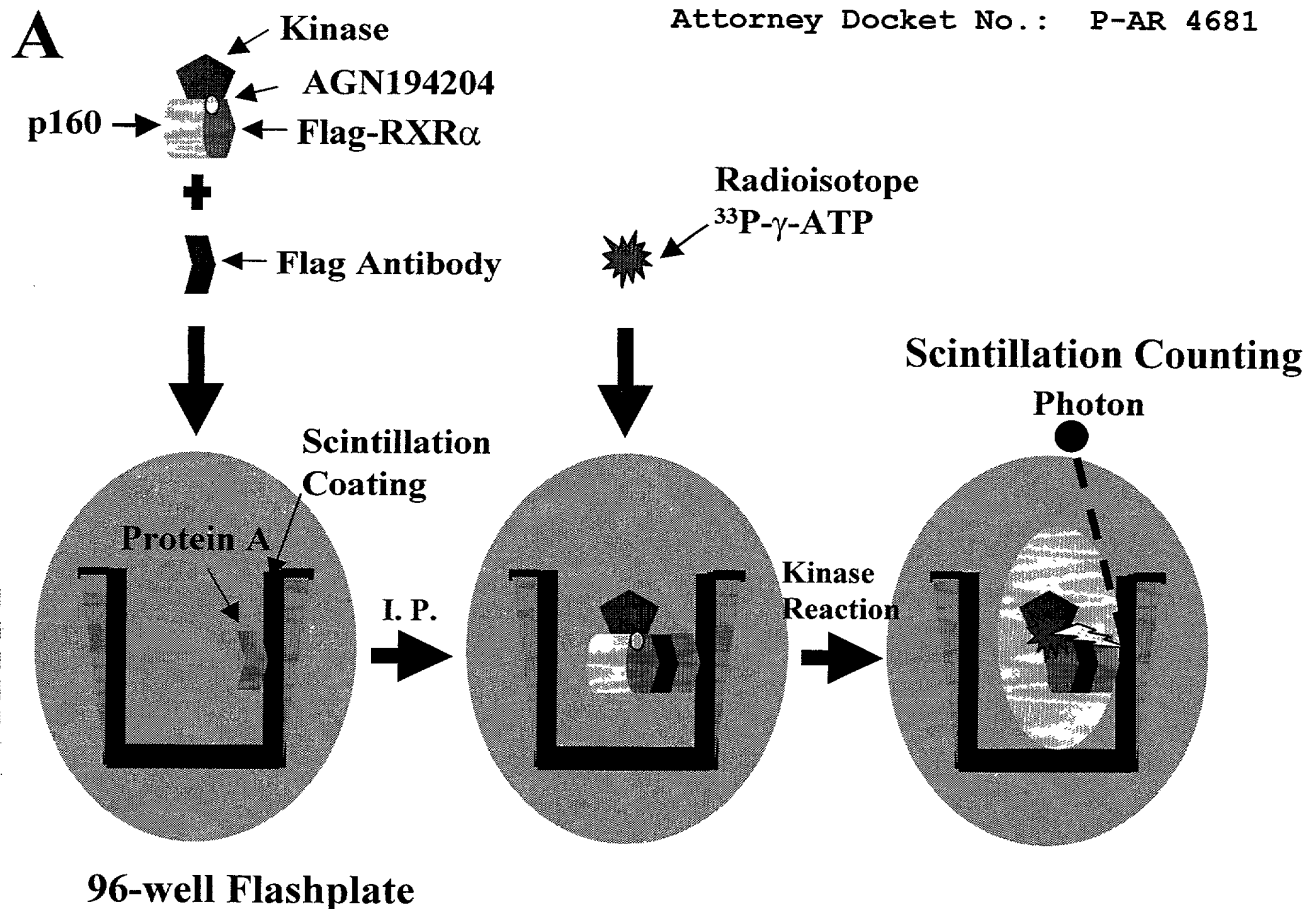
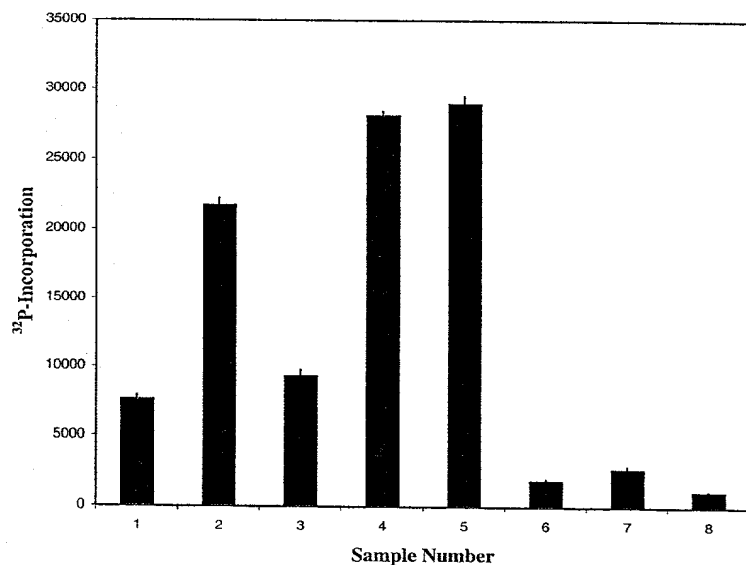


FIGURE 13

A:



B:

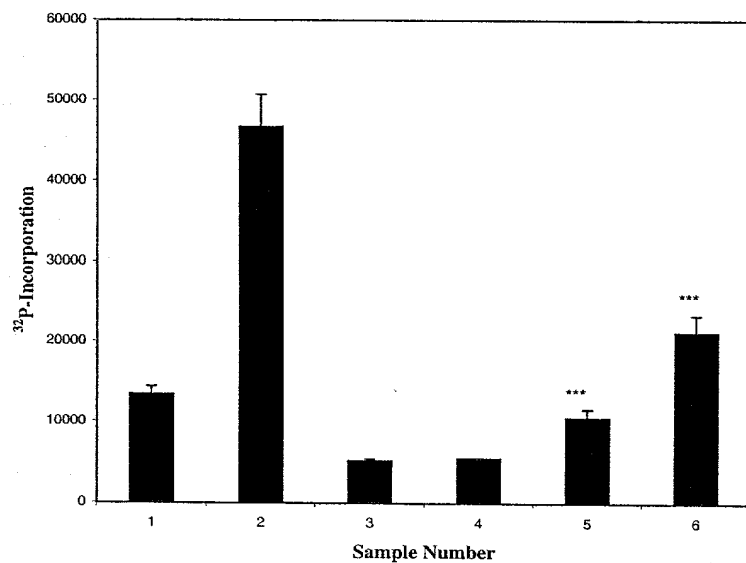


FIGURE 14

C:

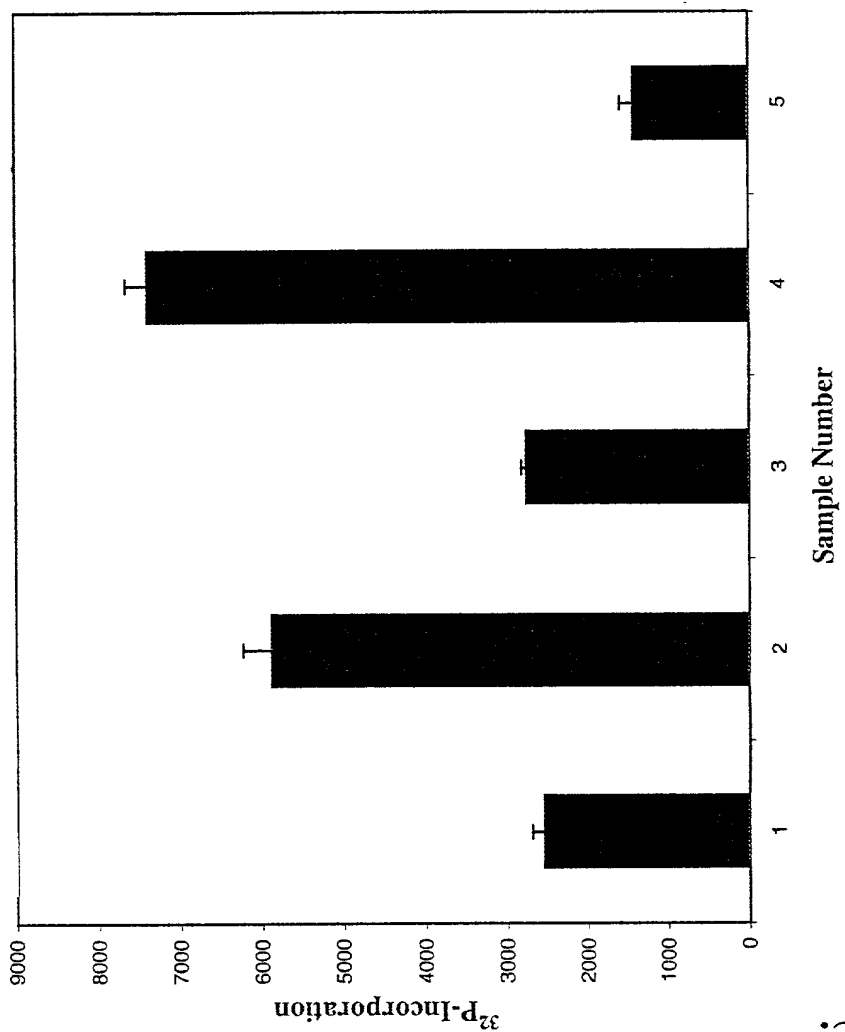
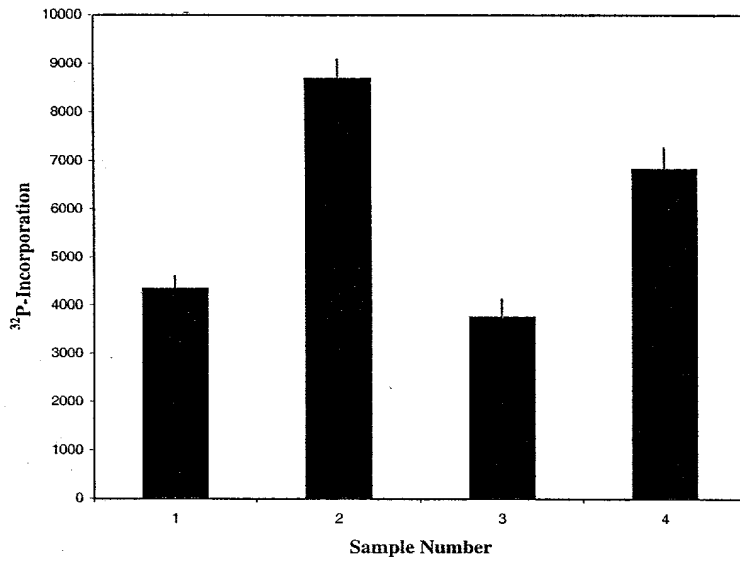


FIGURE 14 CONTINUED

0922226.080201

A:



B:

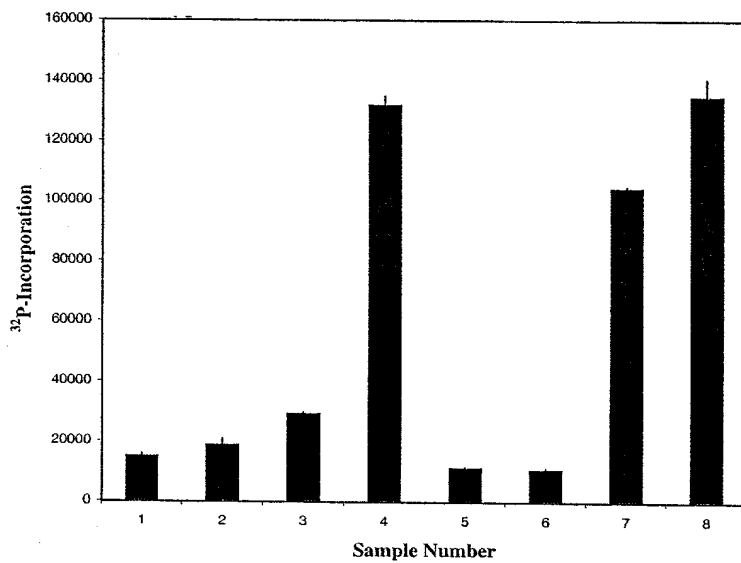


FIGURE 15

FIG. 16

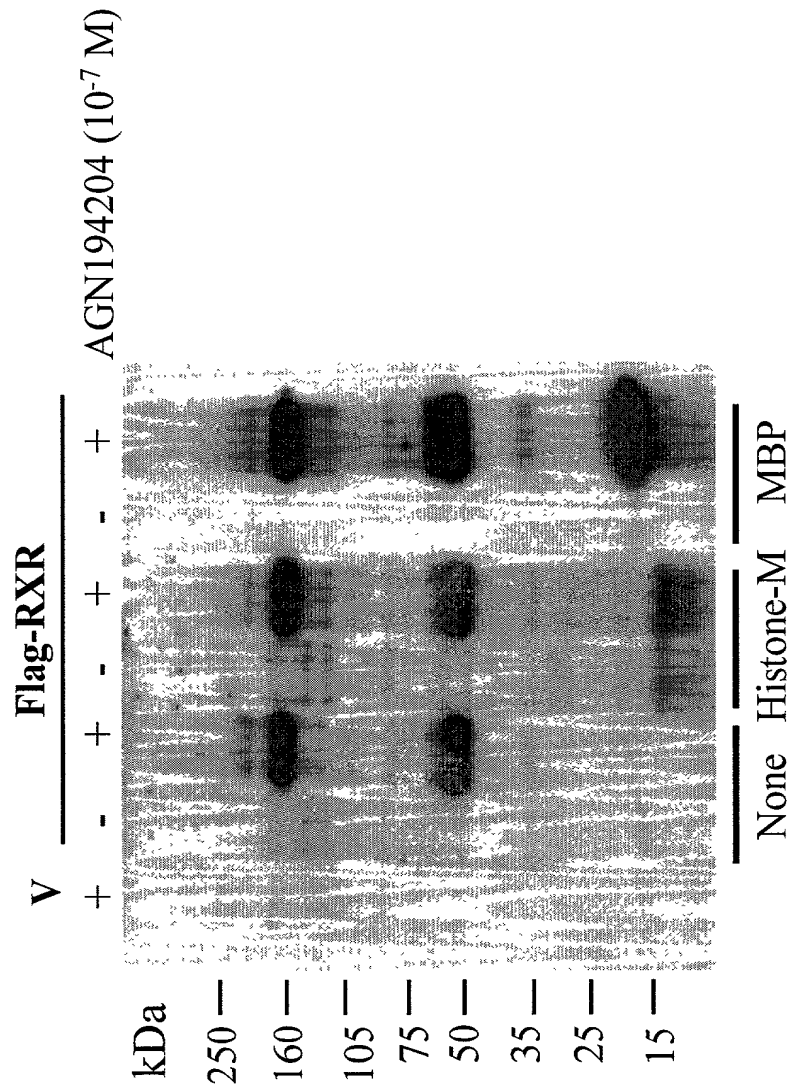
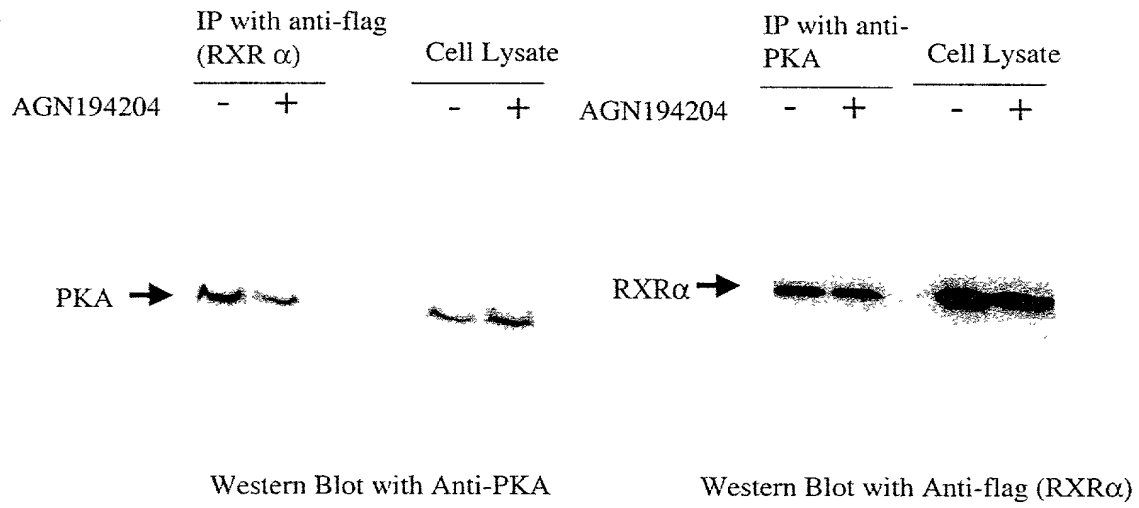


FIGURE 16

A:



B:

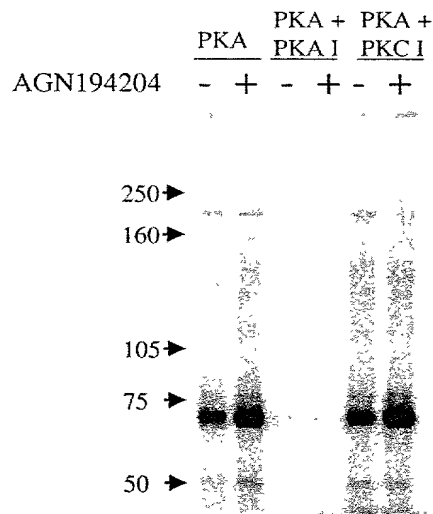


FIGURE 17

Plec-N	..MEPKRIRE	GYLVKKGSV.FNT	WKPMVVLLEDGL	EFYKKK....SD	NSPKGMIPLK
Plec-C	EEFRGVIIKQ	GALLKGGHR.RKN	WKVRKFLREDPAYL	HVYDPA....GA	EDPACAIHLR
RasGAP	DAFYKNIYKK	GYLLKKGKG.KR	WKNLVFLLEGSDACL	IVSESE....KRA	TKPRGLICLS
Akt	.MNEVSVIKE	GALHKKGEY.IKT	WBP YFLLKSDGSFT	GYKERP....E	APDQTLPLPN
Spectrin	TQETPSAQME	GILNRKHEWE	AHNKKASSSS	WHNVVGVENNQEL	GEYKDA....	..KTAASGIP	YHSEVPVSLK
BARK	YALGKDCIMH	CYMSKMGNP.FLTQ	WQRRYFLFPNRL	EWRGEG....EAPQSLTME	
Tiam1-PH1	VRKAGALAVK	NFLVHKKNK.	..KVESATREK	WKHYVSLKGCTL	FEYEID....	..GRSRIDH	NSVPKHAVVW
Grb7	LNAGSFPEIQ	GSLQLRGSG.	...RGSGRKL	WKRFFCFRRSCL	YVSTKG....TSKDP	RHLQYVADYN
Dynamin	NQDEILVLEK	GALTINNIG.IMYGG	SKKEYFVLTAENL	SWYKDD....EE	KERYMESVD
Irs1	TDGFSDEVKV	GYLRKPKS..MHKRFVLA	ASEAGGPARL	EVYENE....	..KKWRHKS	SAPKRSIPLE	
RasGRF-PH1	LLAQRDGTAK	GYLSKRSSD.NPK	WQTRVFAILLQNLL	FYSESD....S	SSRPSGMYLL
RasGRF-PH2	LDTSQTFEIQ	GSLIQVMS <10>	GSLSLK	EGERQCFIFSKHL	IICTRG....	..SGSKLH	LTKNVLSLI
Db1	IGHKKGATKM	KDLARFK....PMQRHLFLYEKAT	VECKRR..VE	SGEGSDRYP	YSFKHCWKMD	
Vav	LANYGRPKID	GELKITSVE.RRS	KTDRYFLLDKAL	LICKRR....GDS	YDLKASUNLH
Sos	GQCCNEFLME	GILTRVCA..KHERHISLFDGL	MICCKSNHGQ	PRLPGASNAE	YRLKEKFFMR	
Bcr	VFLFTDLFLC	TKLKKQSGG.KTQQ	EDTCKVLEPLTDL	SEOMVDELEA	VPNIPLVPDE	ELDALKIKKS
Btk	..MAAVINES	ISLKRSSQK.	..KKTSPLN	SKRRLFLTVHKL	SYVEYD....	..FERGRR	GSCKGSLDME
PLC-delta	DDPDLQAMLK	GSOLLK/KS.SSW	RRERFAQLQEDCK	TINQES....	..RKVMR	SPESQLFSSE
PLC-gamma	VLHLCRSEEV	QVMTLFPYS.	...KKSQRPE	RKTFOVKLETROL	TVSRGA....DKIECAIDR	

Plec-N	GSTSTSPCQD	FGKILMFVFRIT	TTKQQ....	..DHFFQAAF	LEERDAWVRD	INKATKICIEG
Plec-C	GCVVTSVESN	SNGRK	SEENLFSII	TADEV....	..HYFLQAAI	PKERTENIKA
RasGAP	VCSVVVHDS	LFGRLPNCFCIV	VQHFS...EE	HYIIFYAGET	PEQAEWYKGS	QOAFCNLRKS
Akt	NFSVAECQLM	KTERPRPNTFVIR	CLQWT...T	VIERTFHVDS	PDEREEMVRA	DMVANSILKO
Spectrin	BAVCEVALDY	KKKKHVEKIR	LNDGN....	..EYVFOAKD	DEEMNTWILA	ISSAISSDKI
BARK	EIDSVEETQI	KERKCLLLK	IRGGK....	..QFLLQDIS	DPELVQWKE	RDYAREAQQ
Tiam1-PH1	ENSLVQAVPE	HPKKDFVSCS	NSLGD....	..AFLFQTSQ	TELENNIA	ISACAAAVA
Grb7	ENSVVVVTQG	RKLYG	MPTDFGFVK	PNKLR..NGH	KGLHFCSED	EOSTCNVAA
Dynamin	NKLRDVEKG	FMSSKHIFALF	NTEQRNVYKD	YRQLEACET	QEEVDSWKAS	FLRAGVYPER
Irs1	SCFNINKRAD	SKNKHLVAIV	TRDEH....	..EATAAS	EAEQDSWYCA	ELQLHNRKA
RasGRF-PH1	EGSICKRMPS	PKRGTSKES	DKQHIFIVN	FSNDS....	QKSLELRIDD	SKDCDEWVA	TARASYKILA
RasGRF-PH2	ECTELDDPEN	MDDD..GKGQ	EVDHLDKIN	VEPKD...SP	PFTVILVASS	ROEKAANTSD	IIQCMNIRI
Db1	EVCITEYVKG	DN....RKFEIV	YGEKE....	..EVYIVQASN	VDVMTWIRE	IRNILLKQOE
Vav	SFCVRDDSSG	ERDNKKWSHMLI	EDQCA....	..QCYELFFKI	RELKKWMEQ	FEMATSNYYP
Sos	KWLNDDKDDT	NEYKHAFELI	LKDN....	..SVIFSAKS	AEEKNWVAA	ILSLQYRSTL
Bcr	EIKSDIQREK	RANK<19>LL	MSPSMAPVH	SRNGK....	..SVTFLLIS	DYERAEWREN	IREQKKCFR
Btk	KITCVETVVP	ERNP<20>II	ERFPYFFQV	YDEGP....	..LYVFSPI	EEERKWIHQ	ERNVTRYNSD
PLC-delta	EIDEVRMGHR	TEGLEKFARD	IPEDRCFSLV	FKDORN...	..TLDLIABS	PRDAQHWOG	URKILHSGS
PLC-gamma	EIKERIPGKT	SRDF<7>AFR	PQSHCEVIL	YGMEF...RL	KTLSQATSE	..EENMNIKG	IFWLIMEDTLQ

FIGURE 18